CASE REPORTS

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Oat Cell Carcinoma Mimicking Acute Leukemia

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THE CLASSICAL appearance of carcinoma metastatic to bone marrow has been known since the description of Kingsley-Pillers and co-workers.[1] In more recent years, this manifestation of carcinoma has been recognized with increasing frequency,[2,3] especially for oat cell carcinoma of the lung.[4,5] Despite the frequency of occurrence of marrow involvement, severe pancytopenia secondary to carcinoma remains an uncommon event associated with a poor prognosis.[7-9] We present a case of oat cell carcinoma metastatic to marrow accompanied by pancytopenia, which closely mimicked acute lymphoblastic leukemia.

Report of a Case

The patient was a 50-year-old white man first seen at the San Diego Veterans Administration Hospital in August 1976 with complaint of pain on the right side of the chest. At that time, physical examination, x-ray studies of chest and ribs showed no abnormalities, and the patient was discharged on a regimen of oral analgesics. He returned November 1, 1976, complaining of persistent pain on the right side of the chest. Physical examination again showed nothing remarkable except for a fever of 38.5°C (100°F) orally. An x-ray study of the chest now showed a right upper lobe infiltrate and right peritracheal and left hilar masses. Cytological examination of sputum specimens gave positive results for oat cell carcinoma. Results of routine chemistry determinations and complete blood count were normal with the exception of a leukocyte count of 11,700 per cu mm, with a normal differential. Eight to ten platelets were present per high-power field on a routine peripheral blood smear. Smears of a bone marrow aspirate from the right posterior iliac crest showed rare clumps of tumor cells in several smears and the clot section. A right iliac crest needle biopsy specimen showed no evidence of tumor.

Radiotherapy to the mediastinum and right supraclavicular areas was given for relief of pain, and the patient received 2,000 rads (200 rads per day in two weeks) to these areas. During the radiation therapy, the patient's fever abated in response to orally administered penicillin, and x-ray studies of the chest showed improvement; however, his general condition deteriorated. On November 19, 1976, combination chemotherapy was planned, and a pretreatment complete blood count showed a leukocyte count of 6,300 per cu mm; hematocrit, 43 percent; but platelet count of only 36,000 per cu mm. Results of tests for fibrin split products were negative. Because of the rapid supervention of the patient's thrombocytopenia, the possibility of a drug reaction was strongly considered. Administration of penicillin and isoniazid (INH®) was discontinued and a regimen of orally administered prednisone, 60 mg daily, was begun.

After three days of prednisone therapy, the leukocyte count was 5,200 per cu mm; hematocrit, 44 percent, and platelet count 7,600 per cu mm. A repeat right iliac crest bone marrow aspiration and biopsy was done. Smears of the bone marrow aspirate showed complete replacement of marrow elements with immature, "blast-like" cells with a high nuclear/cytoplasmic ratio, and vac-

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uolated and intensely blue cytoplasm (Figure 1). No tendency of these cells to clump was noted. Special stains for periodic acid, Schiff; Sudan black, and peroxidase were negative. Because of the extensive and very rapid total replacement of normal marrow by these immature cells, the possibility of a hematologic malignancy was considered. Results of cytological studies of the patient's sputum were reviewed and were considered compatible with this possibility.

With the patient's informed consent, treatment with cyclophosphamide and vincristine was begun for his original diagnosis, despite his serious thrombocytopenia. Studies of a bone marrow biopsy specimen, available for review two days later, clearly showed normal areas of bone marrow being invaded by foreign cells consistent with oat cell carcinoma (Figure 2). The patient's subsequent course is summarized in Figure 3. The leukocyte count and hematocrit had also begun to fall before therapy, and the former was 3,000 per cu mm on day 1 of his first course of chemotherapy. Administration of prednisone was discontinued, and he received cyclophosphamide, 1.5 grams per sq meter, and vincristine, 2 mg intravenously. The platelet count reached a nadir of 5,000 per cu mm one day after treatment, and he received platelet transfusions. Subsequently the platelet count rose rapidly and he received no further platelet support. The leukocyte count reached a nadir of 835 per cu mm one week after administration of cyclophosphamide was started. He recovered completely from the effects of his pancytopenia and left the hospital with a leukocyte count of 6,000 per cu mm and a platelet count of 180,000 per cu mm. Two weeks after the second marrow aspiration, a third right iliac crest biopsy was done. Attempts at aspiration were unsuccessful, but the biopsy specimen showed extensive fibrosis without evidence of malignancy. Radiation therapy to the lumbar spine for relief of pain had been started two days before the bone marrow aspiration.

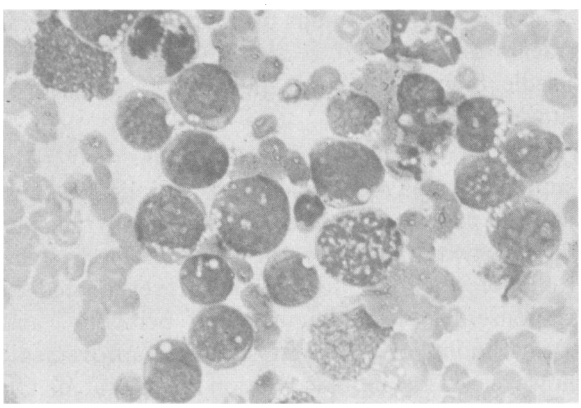

Figure 1.—Smear of the patient's second bone marrow aspirate showing complete replacement by vacuolated, "blast-like" cells. (440×)

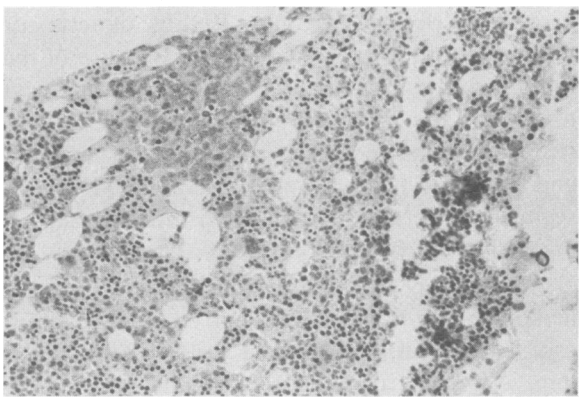

Figure 2.—Representative section of the patient's second bone marrow biopsy specimen showing invasion of normal bone marrow by metastatic oat cell carcinoma. Tumor necrosis was also present (not shown). (440×)

The patient continued to receive methotrexate, cyclophosphamide and vincristine as an outpatient. Bone marrow tolerance was not a problem during his second course of chemotherapy. He was readmitted to the hospital on January 7, 1977, with a rapidly enlarging and painful liver; the complete blood count was entirely normal. He died after a rapid downhill course. At autopsy, extensive involvement by oat cell carcinoma was found in liver, lung and kidney and in abdominal and thoracic nodes. Spinal marrow was found to be normal by gross and microscopic examination. The total course of illness from diagnosis was ten weeks.

Discussion

Metastases to bone from oat cell carcinoma of the lung are a common event without definite prognostic import other than that of disease outside the thorax.[4-6,10] Reported rates of involvement range from 19 percent to 46 percent.[4-6] Severe pancytopenia is not mentioned as a complication of marrow invasion in any of several series reporting successful treatment with combination chemotherapy.[4,6] Rapid onset of severe pancytopenia developed in our patient while he was receiving local radiotherapy for oat cell car-

cinoma. Although initial examination of marrow showed rare foci of tumor cells, a repeat examination showed complete replacement of bone marrow by tumor. The cells seen on smears were large, undifferentiated, vacuolated and "blast-like," showing no tendency to clump. The cells closely resembled those seen in acute lymphoblastic leukemia of childhood or the uncommon leukemic phase of Burkitt lymphoma.[11] Even with a previous cytologic diagnosis of oat cell carcinoma, there was confusion about the cause of the patient's pancytopenia. Serious consideration was given to a concomitant or alternate diagnosis of acute leukemia. A bone marrow biopsy specimen, available several days later, confirmed the diagnosis of carcinoma metastatic to marrow, again demonstrating the complementary nature of bone marrow aspiration and biopsy in this setting.[23]

Complete replacement of marrow by carcinoma has been noted by others, but seldom with smears that so closely mimic those seen in acute leukemia. The recent recognition of the high incidence of involvement of marrow by oat cell carcinoma[4-6] and the routine use of bone marrow aspiration and biopsy as a staging procedure in this disease[5,6] make it likely that such diagnostically confusing smears will be encountered more frequently in the future. Acute leukemia has also been recognized as a complication of chemotherapeutic treatment of other malignancies,[12,13] and it may arise as a complication of therapy for oat cell carcinoma as survival improves in this disease. This case should serve as a reminder that carcinoma, especially oat cell carcinoma, may be associated with pancytopenia and may present a picture similar to acute leukemia on routine smears of bone marrow aspirates.

Depression of bone marrow elements by multiple-drug chemotherapy has been stressed by some authors as the most common and most serious complication of such therapy for oat cell carcinoma.[6,10] However, in this patient, combination chemotherapy resulted in a complete remission of bone marrow disease with return of peripheral counts to normal. Previous reports of successful therapy of severe pancytopenia secondary to carcinoma of the breast or prostate have been restricted to patients who were responsive to hormonal therapy[7,9] or hormonal therapy plus chemotherapy.[14] Kiang and associates[14] have recently reported reversal of even severe marrow fibrosis with splenomegaly secondary to breast carcinoma with combination chemotherapy and hormonal therapy. This case and that reported by Kiang and co-workers illustrate that multiple-drug chemotherapy may be effective in reversing pancytopenia when it is due to extensive marrow

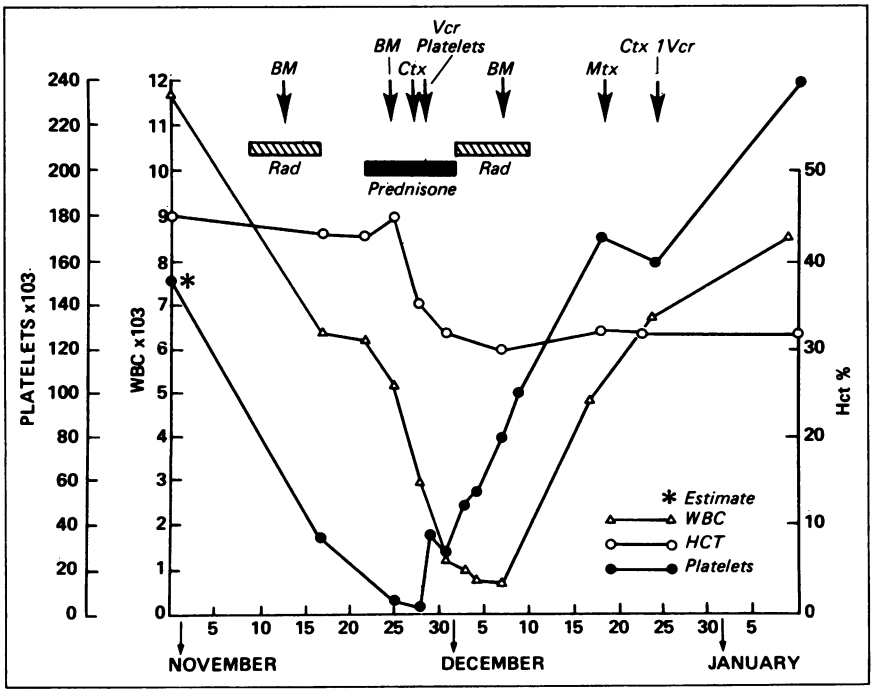

Figure 3.—Hematologic values in a patient with severe pancytopenia secondary to oat cell carcinoma metastatic to bone marrow. Note the rapid rise of both platelet and white blood cell counts after combination chemotherapy.

replacement by a responsive tumor, rather than depression of marrow function by previous chemotherapy. This concept of therapy is commonplace in the treatment of hematologic malignancies and may also become commonplace for carcinoma as response rate and therapeutic indices for these tumors improve.[15,16]

Summary

A 50-year-old man with oat cell carcinoma developed pancytopenia with severe thrombocytopenia while receiving localized radiation therapy. Smears of a bone marrow aspirate revealed complete replacement by "blast-like" cells resembling acute lymphoblastic leukemia. Bone marrow biopsy specimens resolved the diagnostic confusion, showing invasion of normal marrow by carcinoma. Prompt treatment with combination chemotherapy resulted in a complete bone marrow remission, documented with repeat biopsy and subsequently at postmortem examination. This case illustrates how metastatic carcinoma may occasionally mimic acute leukemia causing pancytopenia and replacement of marrow smears with abnormal cells. Pancytopenia in this instance should not be considered a contraindication to chemotherapy.

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Radiation-Induced Disease of the Carotid Artery

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A RARE BUT SERIOUS complication of radiation therapy to the neck is the development of radiation-induced disease of the carotid artery. We wish to (1) present an additional case of radiation-induced carotid artery disease and (2) review the clinical and angiographic findings of this unusual entity.

Report of a Case

A 72-year-old man had a three-year history of dizzy spells, occasionally accompanied by blurred or double vision and lasting two to three minutes. These were brought on by rising suddenly or turning his head rapidly. Nine years previously he had undergone excision of a moderately well differentiated squamous cell carcinoma of the left pyriform fossa together with a left radical neck resection. Postoperatively he received irradiation therapy utilizing a cobalt 60 apparatus to a single left neck portal (14×8 cm). The maximum left neck skin dose was 7,154 R with a calculated tumor dose at 4 cm of 6,045 R given in 42 fractions over 60 elapsed days. At completion of irradiation the residual tumor had disappeared, and the patient has been free of recurrent disease for the past nine years.

On admission the left carotid pulse was absent. A left subclavian bruit was present, and a blood pressure difference was noted between the two arms (right 130/70 mm of mercury; left 108 by palpation). Findings on physical examination were otherwise within normal limits. Angiographic studies showed that a 7-cm, smooth, 95

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